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The emerging significance of nanomedicine-based approaches to fighting COVID-19 variants of concern: A perspective on the nanotechnology's role in COVID-19 diagnosis and treatment

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COVID-19, one of the worst-hit pandemics, has quickly spread like fire across nations with very high mortality rates. Researchers all around the globe are making consistent efforts to address the main challenges faced due to COVID-19 infection including prompt diagnosis and therapeutics to reduce mortality. Conventional medical technology does not effectively contain the havoc caused by deadly COVID-19. This signals a crucial mandate for innovative and novel interventions in diagnostics and therapeutics to combat this ongoing pandemic and counter its successor or disease if it were ever to arise. The expeditious solutions can spring from promising areas such as nanomedicine and nanotechnology. Nanomedicine is a dominant tool that has a huge potential to alleviate the disease burden by providing nanoparticle-based vaccines and carriers. Nanotechnology encompasses multidisciplinary aspects including artificial intelligence, chemistry, biology, material science, physical science, and medicine. Nanoparticles offer many advantages compared to larger particles, including better magnetic properties and a multiplied surface-to-volume ratio. Given this, the present review focuses on promising nanomedicine-based solutions to combat COVID-19 and their utility to control a broad range of pathogens and viruses, along with understanding their role in the therapy, diagnosis, and prevention of COVID-19. Various studies, reports, and recent research and development from the nanotechnology perspective are discussed in this article.

KEYWORDS
COVID-19, nanomedicine, nanotechnology, pandemic, SARS-CoV-2

Introduction

Infectious diseases present a global threat to mankind after a disaster of cataclysmic proportions or a nuclear war. Infectious diseases are the main reason for increasing the morbidity rate, plaguing humanity, and shaping human evolution in the process (Bloom and Cadarette, 2019) and are one of the most important agents leading to premature death, especially in the developing world (Chandler, 2019). Modernization has made mankind complacent about the threat due to the increased access to medical healthcare, vaccines, and sanitization techniques. Sentinel organizations and epidemiological experts have time and again provided abundant warnings about the catastrophe related to infectious disease. Microorganisms do not need a visa to travel to different parts of the world and do not understand geopolitical boundaries. Furthermore, climate change and globalization have aggravated the concern about the spread of infections and pathogens. The newest epidemics such as Ebola, SARS, H1N1, and MERS were an alarming signal for the entire world that the viral pathogens pose a serious threat globally (Vazquez-Munoz and Lopez-Ribot, 2020). The recent pandemic that has hit the entire world is coronavirus disease, commonly known as COVID-19, caused by the SARS-CoV-2 virus (Kaushik, 2021). The virus can be transmitted directly from an infected patient *via* coughing, sneezing, and physical contact. Major symptoms of COVID-19 include fever, sore throat, sneezing, coughing, breathlessness, and tiredness (Figure 1). Moreover, patients having any secondary ailment such as blood pressure, coronary heart disease, or diabetes are potentially at high risk (Rashidzadeh et al., 2021).

Ever since the coronavirus was declared a pandemic on 11 March 2020, many new variants, such as Omicron, Delta, and many more rapidly spreading variants of concern, have posed a major challenge (Cucinotta and Vanelli, 2020). COVID-19 impacted the whole world with the economies collapsing. The first case was observed in December 2019 in Wuhan, where pneumonia-like symptoms were observed in locals. In the first week of January 2020, this new virus was found to be like coronavirus (Ahmad et al., 2020; Sodhi and Singh, 2022).

The surge in cases was exponential further suggesting that the transmission occurs *via* sneezing and coughing from asymptomatic and symptomatic patients. The coronavirus remains on the surfaces for a long period if not destroyed using disinfectants (Koo et al., 2020). As of October 2022, at least 629 million COVID-19 cases and 6.59 million related deaths had been reported globally according to the World Health Organization (https://www.who.int). A certain degree of structural homology and sequence similarity between SARS-CoV-2, SARS-CoV in 2002, and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 was identified (Sadeghi et al., 2021). SARS-CoV-2 transmissibility is higher than that of other viruses (Saylan and Denizli, 2020). The disease severity varies from mild respiratory illness to acute respiratory syndrome affecting the lungs (Chhikara et al., 2020). Infections of COVID-19 can affect the cardiovascular system (Widjaja et al., 2021), kidneys (Esmaeilzadeh et al., 2021), central nervous

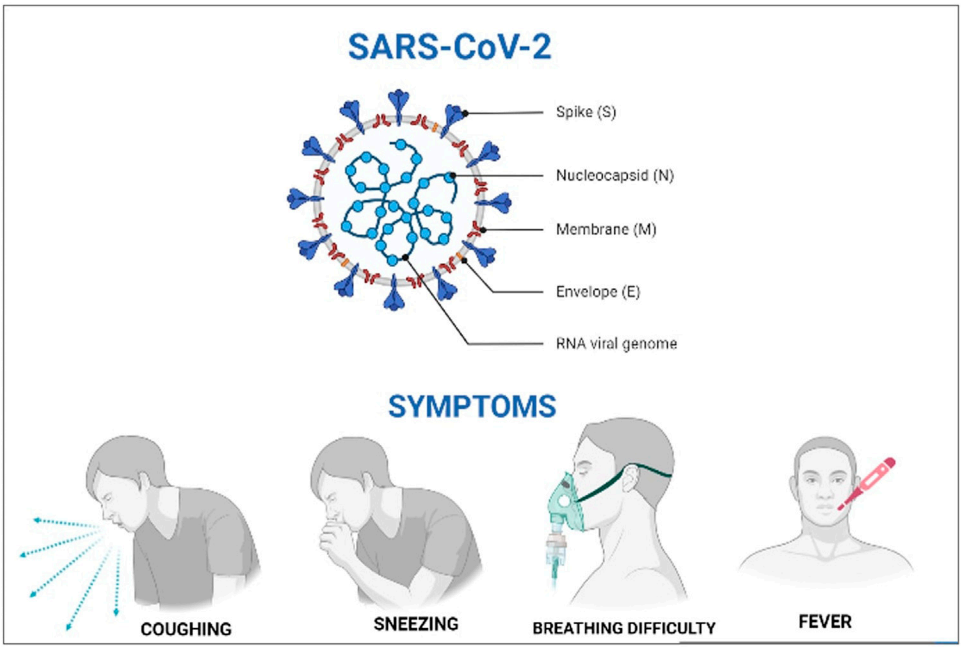

FIGURE 1
Structure of SARS-CoV-2 and the associated symptoms.

system (Esmaeilzadeh et al., 2021), gastrointestinal tract, and liver (Gavriatopoulou et al., 2020). An uncontrolled cytokine storm can lead to the failure of multiple organs, strokes, and heart failure (Rabaan et al., 2021). Many strategies for controlling the infectious disease have emerged, such as lockdowns, social distancing, quarantine, various disinfection protocols, and antiviral treatment methods (Bhaskar et al., 2020).

The conventional treatments of viral pathogenic infections can fade away due to the emergence of novel strains of the virus which emerge because of mutations in the virus (Strasfeld and Chou, 2010). Certain antiviral drugs can be used for the treatment of new strains of viruses (Jackman et al., 2016). However, novel drugs take an extended time to be approved for their safety and efficacy, so the development of new drugs is lagging (Chen et al., 2020). Multidisciplinary research is required for novel approaches for antiviral treatments along with alternative antiviral therapies, targeting the different phases in viral replication (Revuelta-Herrero et al., 2018; Mohammadi Pour et al., 2019). Nanotechnology harnessed immense attention and is explored for possible use in the treatment of viral infections (Szunerits et al., 2015; Singh et al., 2017; Lembo et al., 2018).

The unexpectedness of the SARS-CoV-2 outbreak has retarded the modalities to regulate the damage. The policies including social distancing, unprecedented strict lockdown, vaccination, and wearing face masks have been introduced to control the contagious disease (Chaudhary et al., 2021). Research is focused on modeling innovative point-of-care practices for timely diagnosis and therapeutics to control pandemic-initiated mortalities and morbidities. These strategies are employed, but their success varies spatially and is influenced by environmental factors. Various environmental factors, such as relative humidity, ammonia concentration, and particulate matter, are responsible for the spread of COVID-19 and associated mortality (Bollyky et al., 2022). In the study of Chaudhary et al. (2022a), correlation analysis was used to study the role of environmental factors in the progression and severity of COVID-19. A statistical analysis indicates the correlation between COVID-19-associated mortalities and various environmental factors. The regression model throughout the strategic lockdown has suggested the prominent triumph of unparalleled constraints in Delhi in the form of restrictions on movement. Particulate matter is anticipated to be an important risk promoting the severity and outbreak of COVID-19. The hotspot mapping of airborne ammonia, particulate matter, and relative humidity was also identified using the regression model and mapping the ambient concentration. Areas in the capital undergoing rapid construction, industrial activities, and vehicular emissions are the major hotspots.

Modernization and urbanization can increase the risk of many unseen pandemics in the future. COVID-19 has shaken the world, but still, efficient antiviral treatment options are lacking. COVID-19 presents three major challenges: timely diagnosis, prevention, and treatment (Chaudhary et al., 2021). The major concern worldwide is the determination of an outbreak at an initial stage, which has led to the development of strenuous efforts in the development of point-of-care diagnosis, especially the advanced rapid test, tests based on artificial intelligence, and computed tomography (CT) scans. Forthcoming measures of detection, cure, and prevention have been extensively researched, and advancements have been made using nanotechnology (Chaudhary et al., 2022b). Diverse formulations based on the concept of nanotechnology are considered promising for vaccine development (Cascella et al., 2022). Delivery of nanomaterial-based formulations commends the active agent concentration, silencing RNA, vaccines, antiviral species, and antibodies at the sites of infection generating a basic potentiation of the immune system (Ruiz-Hitzky et al., 2020). Biohybrid nanomaterials are based on polysaccharides and fibrous clay assembly and show a promising environment for viral particles, aiding in their binding to the biohybrid material and helping in conserving their bioactivity. Nanoparticle-based formulations are used in vaccination and for intranasal administration for coronaviruses and influenzas (Al-Halifa et al., 2019).

Nanotechnology has a lot of potentials, and it can be used for the development of medicines and drugs at the nanoscale and can be utilized in the development of novel approaches to deal with viral infections. This can be proved to be a cutting-edge technology that can be used for the successful treatment of COVID-19, but it can also be used to improve the already existing diagnostic and therapeutic strategies (Chintagunta et al., 2021). Nanotechnology is the application of devices and materials in which at least a single dimension is lower than 100 nm. The nanotechnology's application in medicine is called nanomedicine, which comprises the nanomaterials used in the control, prevention, diagnosis, and treatment of diseases (Yayehrad et al., 2021). Nanoparticle research has gained much attention in the last decade due to the advantages of nanoparticles such as small size, multifunctionality, better solubility, adaptability, production of better and safer drugs, nanomedicines, and early diagnosis of diseases (Bhavana et al., 2020; Pandian et al., 2021).

Nanotechnology can help combat COVID-19 by avoiding viral contamination by designing nano-based vaccination for boosting both humoral and cell-mediated immunity, designing personal protective equipment (PPE) kits and disinfectants to increase the safety of front-line workers, designing sensitive and specific nano-based sensors for quick immunological response, and developing novel drugs, having enhanced antiviral activities, sustained release, tissue specificity, and reduced toxicity (Balkrishna et al., 2021).

Nano-formulations can be used to enhance the target delivery and therapeutic efficacy of the antivirals (Singh et al., 2017; Lembo et al., 2018). There is a lack of therapeutic choices for the treatment of viral infections, so plant metabolites offer a

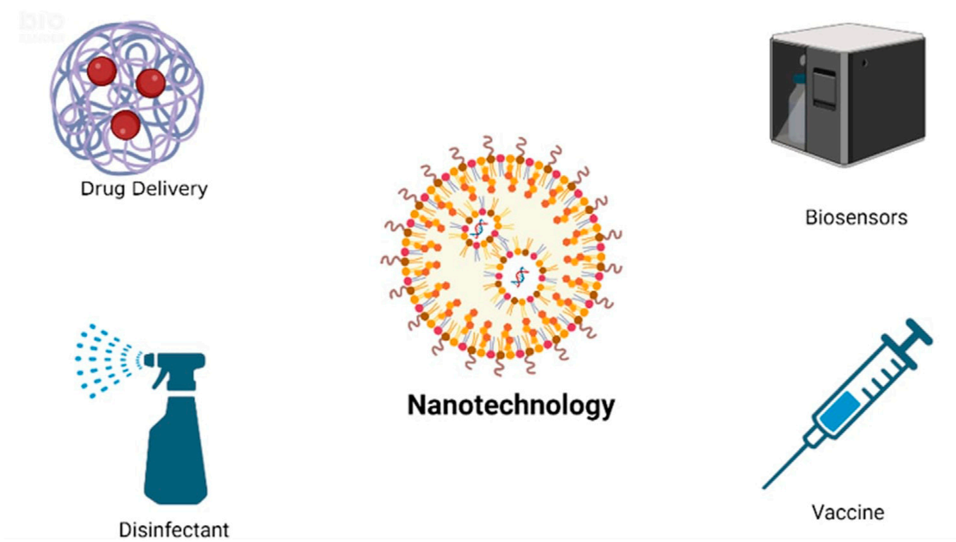

FIGURE 2
Applications of nanomedicine to fight COVID-19.

lucrative option for their treatment. However, plant metabolites have poor solubility and availability, so they are often combined with nano-based carriers for better therapeutic effects (Watkins et al., 2015; Gera et al., 2017; Praditya et al., 2019). Not only in therapeutics but also in diagnostics, many nano-based sensors are used that have high sensitivity and specificity (Mokhtarzadeh et al., 2017). Next-generation vaccines are also available which are based on nanomaterials, offering improved antigen specificity, control release, and target delivery (Vijayan et al., 2019). Delineation of mechanisms involved by which the virus infects the host cell is also carried out (Campos et al., 2020). Figure 2 shows the applications of nanomedicine to fight COVID-19.

Many studies have reported nanotechnology used in the treatment of chronic illnesses such as cancer, but very few studies report their use in addressing the challenges imposed by COVID-19. So, given this, the present review critically discusses various nanotechnology-based diagnostic and therapeutic strategies for managing the SARS-CoV-2 variants of concern.

Role of nanotechnology in COVID-19 diagnostics

Nanostructured systems aid in the advancement of COVID-19 detection, increasing their sensitivity and specificity for signal amplification in a reverse transcription–polymerase chain reaction (RT-PCR) and prophylaxis for vaccines as adjuvants (Krishnan et al., 2021). Nanoparticles play a therapeutic and vital role, especially during different stages of COVID-19 pathogenesis because of the inhibition potential for the preliminary attachment and membrane fusion when the virus enters and in the protein fusion of the infected cell (Vahedifard and Chakravarthy, 2021). Nano-encapsulated antiviral drugs are more effective in the activation of the intracellular mechanism which leads to irretrievable harm to viruses and inhibits the cellular machinery of the viruses by impairing their replication, transcription, and translation. Novel nano-technological methods can help detect COVID-19 infection. A few problems are associated with the already existing protocols; for example, the RT-PCR used for testing the asymptomatic COVID-19 patients was not available in many non-urban centers. The WHO stated the urgency for novel diagnostic kits for detecting SARS-CoV-2 (Kamat et al., 2021; Fernandes et al., 2022).

COVID-19 detection using loop-mediated isothermal amplification

Loop-mediated isothermal amplification is a rapid method that has high specificity and sensitivity (Kim et al., 2022). Xu J. et al. (2020) showed that magnetic nanoparticles can be used in RT-PCR diagnosis and for extracting SARS-CoV-2 RNA. Magnetic nanoparticles are used in this technique which are functionalized with poly amino ester, and the extracted RNA was absorbed on magnetic nanoparticles containing carboxyl groups. The interaction of the RNA magnetic nanoparticle and carboxyl groups is used for the analysis (Xu L. et al., 2020). They are directly used without the elution of viral RNA from the magnetic beads. It is a time-saving mechanism and protects from any contagious risks. The magnetic nanoparticles were used by the same group in a different study, where the virus was isolated instead of eluting viral RNA. The enriched viral particles are bound tightly to nanoparticles because of target receptors. The magnetic nature of the nanoparticles is attained by the encapsulation of paramagnetic iron oxide. They help in the detachment of the virus from nanoparticles with the aid of an external magnet and detect the virus by immunochromatographic strip tests, cell-based tittering assays, and quantitative RT-PCR (Mujawar et al., 2020; Shan et al., 2020).

Fifth-generation biosensors for COVID-19 detection

Current health crises because of infectious diseases including COVID-19 and monkeypox have raised the model of multifunctional and portable biosensors embedded in the solo chip. Conventional diagnostics methods are costly, complex, and time-consuming; therefore, biosensors are used as a lucrative alternative as they possess applications in the pharmaceutical and healthcare industries (Verma and Bhardwaj 2015). Biosensors are installed for the recognition of multiple diseases, prevention, health observation, and rehabilitation of patients (Dwivedi et al., 2021). The fifth-generation biosensors can be used for studying advanced nanomaterials, and they can be integrated with intelligent and rapid data processing strategies and packed in portable modules for various healthcare applications (Wu et al., 2022; Zhang et al., 2021). Biosensors aid to integrate the pioneering functional materials having manageable physicochemical attributes and ideal machine processability. The 2D metal nitrides and carbides show promising performances due to their adjustable physicochemical properties and rich surface functionalities. The biosensor hybridization along with diversified nanomaterials provides challenges for the commercialization of stability due to oxidation. Biosensors have been interfaced with modern-age technologies, including 5G communication and artificial intelligence (AI), for heading toward the hospital-on-chip (HOC) modules. Graphene and its derivatives, metal nitrides and carbides (MXenes), and borophene have emerged as excellent biosensing platforms with a high specific surface area with enhanced detection and monitoring efficacies (Zhang et al., 2021; Chaudhary et al., 2022a; Chaudhary et al., 2022c). MXenes demonstrate enormous potential for monitoring and detecting diverse biomolecules and encompassing electrochemical, optical, and plasmonic modules (Sheth et al., 2022). The infectious and fatal diseases have certainly burdened the already existing healthcare services globally and resulted in mortalities, so the primary concern in the post-COVID-19 era is the early diagnosis of contagious diseases to strengthen their treatment and curtail the spread (Chaudhary et al., 2022b; Noh et al., 2022). The consequences of infectious diseases can be managed *via* early diagnosis of respective biomarkers, so as to enhance their therapeutic efficiency (Cherusseri et al., 2022; Markandan et al., 2022). Timely detection *via* point-of-care (POC) diagnostics is highly advantageous, as it is highly efficacious and simple. Nanomaterials can also be utilized to enhance the functioning of the POC devices for improved efficiency. Table 1 and Figure 3 show the use of nanotechnology in the prompt diagnosis of COVID-19.

Nanomedicine's role in COVID-19 treatment

Nanomedicine influences every field of medicine and is a dynamic tool for the development of novel therapeutics, medical imaging, nanotherapeutics, vaccines, and biomaterials for the regenerative medication (Varahachalam et al., 2021). Nanomedicine is an amalgamation of nanotechnology and medicine and uses nanoparticles in therapeutic or diagnostic applications (El-Sayed and Kamal, 2020). Soft nanomaterials are attained from lipids, proteins, polymers, and surfactants and are often applied in nanomedicine for drug delivery. There are also prerequisites for the use of nanomaterials (Devadasu et al., 2013). Several drug-based nanoparticles are under clinical trials for diseases such as neurodegenerative diseases, cancer, cardiovascular, infectious, and inflammatory illnesses (Yetisgin et al., 2020). Nanoparticles can aid in active or passive drug targeting along with controlled drug release, which affects the safety and efficacy of the treatment. Metal nanoparticles can be used in nanomedicine, due to their antibacterial, antiviral antifungal, and antiparasitic activities (Singh et al., 2019). Pathogenic bacteria develop resistance to already used antimicrobials, which led to the development of nanotechnology-based antimicrobial therapy, such as metal-based antimicrobials, which are effective in the treatment of superbugs. Similarly, the incidence of a new strain of viruses and heterogeneity has likewise necessitated advanced and innovative therapies. Since nanotechnology offers specific targeting, it can be used for antiviral therapy (Teixeira et al., 2018).

Nanoparticles can be used to combat SARS-CoV-2 by targeting mechanisms that affect the viral entry inside the host until they get activated. By blocking the surface proteins on the virus, the virus gets inactivated, so nanoparticles are designed specifically for virus-expressed proteins and could diminish viral internalization (Goscianska et al., 2022). Metal nanoparticles can block the virus's attachment to the host cell, thereby inhibiting the internalization of the virus and impairing the replication of the virus during viral entry. Silver (Ag), titanium (Ti), zinc (Zn), and gold (Au) have shown results against the influenza virus, herpes simplex virus, transmissible gastroenteritis virus, Zika virus, HIV, and monkeypox virus (Mainardes Diedrich, 2020).

TABLE 1 Use of nanotechnology in the prompt diagnosis of COVID-19.

S. No.	Technique	Application	Reference
1	Point-of-care testing	• Used to diagnose infected patients without transporting the samples to the laboratory	Konwar and Borse (2020); Xu J et al. (2020); Asif et al. (2020)
		• Colorimetric biosensor centered around paper-based DNA is used for detecting the virus very rapidly in the sample	
		• The paper-based sensor uses a cationic pyrrolidinyl peptide nucleic acid (PNA) having better hybridization than RNA and DNA probes. The presence of lysine in the probe imparts a positive charge and interacts with the silver nanoparticles along with negatively charged DNA	
		• PNA particles can bind to the silver nanoparticles causing the aggregation of the nanoparticles if viral RNA/DNA is not present, whereas when viral RNA/DNA is present, a complex is formed with the COV virus without any nanoparticle aggregation	
2	Chiral biosensors	• Chiral zirconium quantum dots are utilized for COVID-19 detection. The formulation contains zirconium quantum dots, magnetic nanoparticles, and antibodies specific to the coronavirus	Ahmed et al. (2017)
		• The magnetic nanoparticles and zirconium dots bind to the virus strongly, and magneto-plasmonic fluorescence is displayed if the virus is present	
		• The external magnets are used to separate the magneto-plasmonic-fluorescent nanohybrids to measure the fluorescence intensity to detect the presence or absence of the virus	
3	Electrochemical biosensors	• A slight modification of the electrochemical sensing process is performed using the gold nanoparticles which aid to retain the functional moiety of the biomolecule	Martínez-Paredes et al. (2009); Ishikawa et al. (2009)
		• Gold nanoparticles play a role in the interface as it acts as an electrocatalytic material	
		• Carbon electrodes are utilized to coat the gold nanoparticles and as an immunosensor in one of the studies, where immobilization of spike S1 protein of COVID-19 is performed using the gold nanoparticles and the immobilized protein can interact with the SARS-CoV-2 in the sample and can bind to the antibody in the sample	
		• In the absence of SARS-CoV-2, the antibody in the sample can bind to the spike protein and a reduction in the peak current can be observed, but in the presence of the virus, the antibody in the sample will bind to the immobilized antigen	

Organic nanoparticles are used to improve the bioavailability of the antivirals such as dapivirine, zidovudine, efavirenz, and acyclovir. The organic nanoparticles are also important to promote effective drug delivery and help in targeted antiviral delivery (Delshadi et al., 2021). Nanoparticles overcome antiviral limitations to specific targeting which results in cytotoxicity of the host cell. Many clinical trials have been conducted for COVID-19, and antimicrobials like ribavirin, lopinavir, remdesivir, chloroquine, and ritonavir were tested and showed promising results against SARS-CoV-2 (Oroojalian et al., 2020). Nanoencapsulation of these drugs may aid in the development of safer treatments for viral diseases such as COVID-19. The nanoparticles in the case of viral diseases are underused and not fully explored, which came to light during the pandemic (Pandey et al., 2020).

Nanomedicine can deliver a general platform that can be improved simply to ensemble the application in necessity. This can be displayed during this brief span since the pandemic started. For example, with the change in the therapeutic particle encapsulated inside synthetic or natural nanoparticles, a different vaccine for the treatment of COVID-19 can be developed. Specific regulations are lacking for the approval of

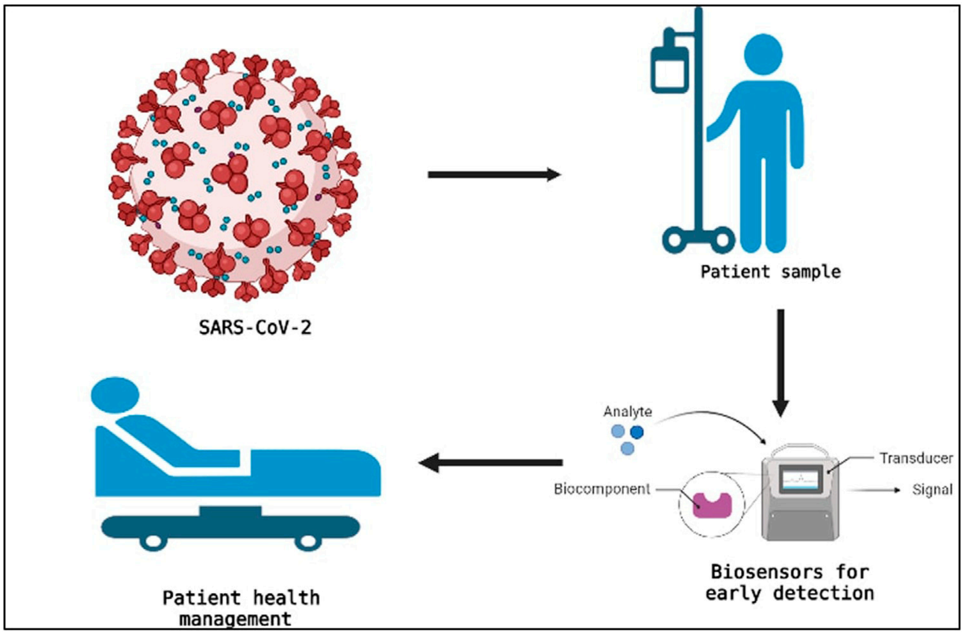

FIGURE 3
Rapid diagnosis of COVID-19 using biosensors.

nanomedicine, and novel nanomedicine must undergo full clinical trials (Germain et al., 2020). During the hard times amidst the coronavirus, nanomedicine has outshined other fields, and the knowledge has provided science with innovative therapeutic modalities for the pandemic. The clinical development of nano-products is necessary to solve the clinical needs which are beyond oncology. It is vital to report the lacunae facing the development of nanomedicine such as aspects, especially related to the nanotoxicology of new nanomaterial classes along with the global explanation on monitoring approval for both the biological activity and physicochemical characterization, especially for multifunctional products (Hashemi et al., 2021).

Nanomedicine with a size of up to 200 nm is a beneficial cargo fabricated using a suitable drug nanocarrier as a beneficial agent (Moghimi et al., 2005; Karimi et al., 2016). Magnetic nanoparticles can be used to control and manage the virus pathogen even in the brain as nanomedicine can cross any barriers *via* the following measures: 1) nanomedicine functionalization with specific receptors for the brain, 2) using ultrasound as external stimulation, and 3) a non-invasive method which can use a magnetic drug delivery system (Mitchell et al., 2021; Mohammadi et al., 2022). Magnetic nanomedicine is designed to deliver the drugs at a specific site to control release by applying peripheral stimulation like a magnetic field, and the drug release sequence can be strategized according to the prerequisite of the disease condition (Ashwini et al., 2022; Naghdi et al., 2022).

The nanomedicine performance depends mainly on the choice of a multifunctional stimuli-response drug nanocarrier, opto-magnetic, magneto-plasmonic nanosystem, and magneto-liposome (Kaushik, 2021). Nanomedicine can be vital for the recognition of disease progression and drug distribution. Manipulative magnetic nanomedicine (MMN) is a possible upcoming therapy wherein control over delivery and routine is mandatory (Kaushik, 2021). MMN can aid in the identification and elimination of the SARS-CoV-2 virus for the management of viral symptoms and infection. In addition to the elasticity in using the therapeutics of the choice, these unscrupulous nanomedicines can be recognized as a long-interim treatment for the SARS-CoV-2 infection, where immune supportive agents can stay for a long period in the body without fabricating any ill effects. MMN proves to be a compulsory remedy, and emphasis on its expansion must be made by the forthcoming study with the resulting objectives: 1) exploration of stimuli-responsive MMN for precise delivery and release; 2) confirmation of the site of drug delivery and release by using image-guided therapy; 3) delivery of drug in the gut and blood–brain barriers using the magnetic guided approach; and 4) the customization of MMN according to the medical history and disease profile of the patient, for example, selection of CRISPR-Cas and anti-SARS-CoV-2 virus based on the genomic profiling of the patient (Kaushik, 2021). The customization of the MMN for extended therapeutics allows the release of the drug for a longer time to manage post-COVID-19 effects (Jayant et al., 2018; Kaushik et al., 2018; Kaushik et al., 2019; Tomitaka et al., 2019; Kaushik, 2021).

SARS-CoV-2 infection is a manifestation of many symptoms. COVID-19 infection requires extensive treatment, and even after discharge from the hospital, the patient may have the complicated condition for a longer time (Dao et al., 2021). Conventional antiviral drugs cannot be used for the treatment of adverse symptoms. Micro-needle-based vaccine delivery is used for the management of COVID-19 infection. Initial trials are promising, but a lot more must be carried out for animal-based trials, followed by FDA approval. MNM can be promoted against COVID-19 effectively, and research is required in this field to traverse the path from *in vitro* to *in vivo* and finally to clinical and human trials, and FDA approval is required for public use. For the development of anti-COVID-19 infection therapy, critical safety-related risk assessments should be assessed. Artificial intelligence introduction can be a good option, because of the use of bioinformatics to perform big data analysis and avoid hit-and-trial approaches (Gage et al., 2021; Kaushik, 2021).

Artificial intelligence-based face masks to combat COVID-19

Since the old civilizations, face masks are a vital component of human lives. Face masks are used as an economically viable tool and create a sense of communal unity and combat health hazards (Chaudhary et al., 2022d). The use of face masks is still not normalized because of manufacturing limitations, solid waste production, and unawareness. The limitations have been overcome by the choice of material utilized for manufacturing (Ganesapillai et al., 2022). Masks are designed from textiles such as biomaterials and nanomaterials in the present-day market. Face mask respirators (FMRs) are engineered using nanomaterials and are advantageous as they have a high specific surface area, unique physicochemical properties, multiple usages, good breathability, and pathogen-detecting and -scavenging capabilities (Forouzandeh et al., 2021). FMRs are vital as they break the chain of viral infection, thereby protecting the community spread (Chaudhary et al., 2022a). The SARS-CoV-2 viral infection is correlated with fungal and microbial infection. Mucormycosis spread in various countries is a consequence of COVID-19. The variants of concern like Omicron have a higher spread rate and have challenged the diagnosis, prevention, and therapeutics for COVID-19 (Bhatt et al., 2021). More novelties, especially in designing the preventive FMRs are crucial with intelligent and smart features. The inclusion of the contemporary technologies of nanotechnology, Internet-of-Things (IoT), artificial intelligence (AI), and machine learning can be useful in architecting the FMRs (Umapathi et al., 2021). The IoTs can be used and integrated with nanomaterials for the fabrication of next-generation FMRs having AI techniques. The sensors can also be incorporated into the FMRs to observe human behavioral and physiological signals. Even in the remotest part of the world, nanomaterial-based biosensors can be integrated into FMRs using minute radio antennas used for the diagnosis of COVID-19 (MacIntyre and Chughtai et al., 2020). The radio antenna integrated into the FMRs can aid in the recording of COVID-19 cases. The integration of AI makes the technology available to any user and helps in the management and monitoring of COVID-19. With the help of AI, smarter FMRs can be designed and can control the massive spread of COVID-19 (Manickam et al., 2022). The Global Positioning System (GPS) should be incorporated to assess the patient's routine and set up early warnings and advice (Chaudhary et al., 2022b). A smart filtering facepiece (FFP2) mask with an opto-chemical sensor integrated and driven *via* a smartphone is used for monitoring CO_2 inside the mask. This mask is fabricated specifically to tackle the health effects that arise due to prolonged use of the face mask. Chen et al. (2022) reported the use of an FMR based on electrospun polyetherimide (PEI) electret non-woven. It is a bi-functional mask that removes particulate matter and is also used for the generation of electricity. It is capable of self-sterilization and has features such as biodegradability, transparency, breathability, hydrophobicity, and biocompatibility (Chen et al., 2022).

Application of 3D printing to combat COVID-19

The demands for medical technology have exceptionally increased since the arrival of the global pandemic. Innovative 3D printing, which was initially started with no practical utilization, has now been accepted in various industries, for example, engineering and healthcare (Larrañeta et al., 2020). Three-dimensional printing is used to produce face shields, components of the ventilator, and masks which were of utmost importance during the pandemic scenario. In this technique, products are fabricated utilizing digital CAD files using layer-by-layer techniques (Munaz et al., 2016; Irfan Ul Haq et al., 2020). It is highly favored in the medical field because of its customization. This technique is beneficial as it helps in adapting to variations as per the circumstances of the patient (Marro et al., 2016). The software helps in conceptualizing medical equipment, which is later 3D-printed with less cost and time. The rapid prototyping of this technique permits a rapid mobilization of the equipment (Marro et al., 2016).

A 3D antibacterial swab made up of a bio-cellulose lattice structure is used for the detection of COVID-19 as the use of a nasopharyngeal swab poses a serious problem. Nasopharyngeal swabs which are 3D-printed deliver a lucrative and fast substitute as compared to conventional nasopharyngeal swabs (Haleem et al., 2021). Three-dimensional printing is vital for hospitals as it

TABLE 2 Nanomedicine formulations for the COVID-19 therapeutics.

S. No.	Formulation	Application	Reference
1	Nano-sponges	Nano-sponges' formulation is one significant development in the field of nanomedicine. The nano-sponges are made up of nanoparticle cores, encircled by cellular membranes. A three-dimensional network offers many advantages such as superior drug absorption and complexation and slow degradation. Molecular built-up and assembly of nano-sponges allows the drug co-encapsulation for effective and direct treatment. For example, the pore-forming toxins (PFTs) can disturb the host cell membranes and increase the permeability. It is important in bacterial infections and is a part of the virulence control mechanism	Swaminathan et al. (2016); Tannous et al. (2020)
2	Nanoparticle-based drug therapy	In nanomedicine, nanoparticle-based drug therapy is an advanced technology. It improves the therapeutic indices by, for example, increasing the immunogenicity, bioavailability, solubility, diffusivity, and controlled and targeted release of the drug *in vivo*. Copper nanoparticles can enhance the efficacy of remdesivir and arbidol which can treat COVID-19	Patra et al. (2018)
3	Nanoparticle-based gene therapy	Gene therapy deals with the replacement or deletion of "defective" genes in the unhealthy cell. Recombinant nucleic acids containing therapeutic genes result in blocking the translation of mRNA, resulting in reduced disease progression. Nucleic acids such as microRNA (miRNA) and small interfering RNA (siRNA) are used for the purpose. Clustered regularly interspaced short palindromic repeats (CRISPR) technology has reformed treatment for COVID-19. Use of Cas9, a nuclease derived from bacteria is used to fix precise point mutations on a target gene	Wei et al. (2020)
		The major challenge is in the innocuous and precise delivery of CRISPR-Cas9 to the target site, and nanomedicine is a possible solution. Copper nanoparticles are a good option for the CRISPR-Cas9-mediated gene therapy delivery to target lung tissues damaged due to SARS-CoV-2	

is remarkably positioned to elucidate the instant needs and acts quickly on them by operating together between industry and hospital and helping in saving valuable time to address the shortage needs in hospitals (Javaid & Haleem, 2021).

Three-dimensional-printed face masks are vital. One example is the Copper3D NanoHack mask which creates the borders of the community-created tactics and the necessity for the improvement of design which is based on the availability of the technical base and local testing. A polylactic acid (PLA) filament is used for 3D printing, and it is hand-assembled into the final 3D configuration when heated at 55–60°C through a hair dryer or hot air (Belhouideg, 2020). The mask consists of a simple port for air intake with the insertion of two reusable filters, and the filter can be kept in place by a screw-in cover (Tino et al., 2020). PPE is also used in 3D printing. The pandemic significantly increased the use of PPE, especially its use in healthcare has significantly increased. There is a surge in the propagation of the 3D printing method mainly due to an increase in the ability to produce PPE *via* organized means.

Three-dimensional printing offers many advantages, but there are also a few limitations to 3D printing (Clifton et al., 2020). The major problem is that the mechanical hindrance of particles can only be simulated to a degree, but the multiplication of the electrostatic properties of the filter with 3D materials is a major challenge. Thermoplastic filaments which are essential for fused deposition modeling (FDM) printing vary extremely in the composition of materials, porosity, and environmental stability (Katkar et al., 2018). FDM filaments grasp ambient moisture, which could stance an absurdly amplified risk for virus transmission during reuse (Jurischka et al., 2020). Table 2 shows the nanomedicine formulations for the COVID-19 therapeutics.

Challenges to the use of nanotechnology in COVID-19 treatment

Respiratory infections are one of the most common reasons for deaths worldwide. Although there are vaccines and drugs available now to prevent or treat COVID-19, many existing drugs are repurposed drugs that are effective against very few pathogens (Saha et al., 2020). Along with the conventional approaches, researchers are trying to develop suitable nanomedicines. This review highlights the role of nanomaterials in diagnosis, prevention, and vaccine production, and their role in the treatment of patients relapsing after finishing a conventional antiviral treatment (Yetisgin et al., 2020). Nanoparticle development is a lucrative option due to its surface charge, shape, size, large surface-to-volume ratio, and biological and functional properties. The conventional therapies do not appear to be well-equipped in handling the pandemic. Therefore, we must prioritize diversifying our research to seek a permanent solution that can fight future pandemics. Nanotechnology can help develop measures to reduce SARS-CoV-2 infectivity and help in prompt diagnosis of the contagious disease (Harish et al., 2022). Sanitizers based on nanotechnology display a broad and potent antimicrobial and antiviral activity; therefore, they can be instrumental in improving safety and uplifting healthcare facilities, especially in developing countries (Sportelli et al., 2020). Nanotechnology plays a crucial role in the design of detection kits, vaccines, and therapeutics to fight the COVID-19 variants of concern. The therapeutic use of antiviral drugs based on nanotechnology is an effective remedial option; as more research options are accessible, it can further be expanded (Varahachalam et al., 2021). The antimicrobial potency of drugs can be enhanced using nanomaterials for the treatment of secondary infections. Nanotechnology along with *in silico* drug designing, artificial intelligence, and synthetic biology is still in a nascent stage, especially with regard to their applications. Most of the translational research on nanotechnology and other promising domains is utilized for diseases such as cancer (Kamat et al., 2021). Nanotechnology offers many limitations in managing COVID-19, as it fails to eradicate viral particles within the body. The lack of research to study the *in vivo* behavior of these nanoparticles inside the body, the immunological response to these nanomaterials and their systemic clearance, and side effects is not well understood (Rai et al., 2021). With the severity of the ongoing pandemic and the sudden damage it has caused, many nations are unwilling to risk their resources on unconventional technologies. RNA viruses are prone to mutations and recombination which makes them more dangerous to humans and can be considered a global threat (Hu et al., 2021). Nanomaterials, especially due to their nano-size can cause respiratory ailments and lung problems, and this aspect should be kept in mind while designing the nanoparticle. Oxidative stress, fibrosis, immunotoxicity, inflammation, potential cell toxicity, and genotoxicity of the nanoparticles are important issues that must be solved before reaching patients (Di Giampaolo et al., 2021).

Conclusion

Academia and research industries all over the world are working to alleviate the health crisis caused by COVID-19. Nanoscience and nanotechnology tools offer a useful approach to the present global priority. Basic research, which starts from the computational simulation to study the interaction of the virus with nanomaterials, is vital to obtain data on the viral particle's nanostructure and their mechanisms of infection. Safe and judicious use of nanomaterials is vital, as almost all the studies conducted so far have evaluated the treatment using only the *in vitro* approaches. Nanomaterials' behavior and fate can change upon reaching blood circulation. Thus, we should rely on *in vivo* models for long-term exposure to comprehend the behavior of the nanoparticles in the body. There is a need to accelerate the deployment of suitable approaches which can be used to prevent, diagnose, and treat infectious diseases. Advances in the treatment and diagnostics of COVID-19 are continuing quickly, but novel viruses such as coronavirus and their mutants are more aggressive than the typical flu. Antiviral drug cocktails helped patients with moderate COVID-19 symptoms and stopped the multiplication of the virus. The use of nanocarriers can help in the transportation of these drugs, and their administration through the nasal route could save many lives. Nanotechnology advancement provides a lucrative solution for the rapid detection of the infection and helps to develop antigen and antibody testing kits that are useful, especially for asymptomatic patients. Lipid nanoparticles, viral-based vaccines, hard nanomaterials, which are used for viral detection, and the fabrication of PPE are at the lead in the pandemic. These technologies stemming from nanomedicine are very promising and lay the platform to deal with unforeseen pandemics in the future. It is a big push for the application of nanomedical technologies and eventually becomes an incentive for industry stakeholders, funding, and regulatory bodies to invest further in this budding field. Continuous research is required to improve the characteristics of these diagnostic, preventive, and therapeutic modalities *via* the use of nanotechnology which is the primary focus of the researchers. Researchers identifying the nanomaterials for medical sciences must warrant that nanomaterials can deal with any future pandemics.

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CKS: writing and editing. KKS: conceptualization, writing, editing, and supervision.

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Conflict of interest

The reviewer VC declared a shared parent affiliation with the authors to the handling editor at the time of review.

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Publisher's note

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